# Clinical Breakpoints for Antimicrobial Agents in Pulmonary Infections and Sepsis: Report of the Committee for Japanese Standards for Antimicrobial Susceptibility Testing for Bacteria

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## I. BACKGROUND

The Committee for Japanese Standards for Antimicrobial Susceptibility Testing for Bacteria, Japan Society of Chemotherapy, (chairman: Sachiko Goto, MD, Table 1) established the standard method of the Japan Society of Chemotherapy for microdilution antimicrobial susceptibility testing of bacteria that grow aerobically.[1] Furthermore, the Committee (chairman: Atsushi Saito, MD) determined the standard method for microdilution antimicrobial susceptibility testing methods for bacteria that grow anaerobically and for bacteria that require special nutrients.[2] At the 41st All Japan meeting for the Japan Society of Chemotherapy (Tokyo, 1993), the Committee proposed clinical breakpoints for antimicrobial agents which could be used in pulmonary infections and sepsis, soliciting opinions from the members of the Society. The originally proposed breakpoints were partially revised and here we submit the breakpoints in pulmonary infections and sepsis as authorized by the Japan Society of Chemotherapy.

It would be ideal if breakpoints for antimicrobial agents in any organ could be determined with the measurement of MIC (minimum inhibitory concentration), a quantitative designation of drug susceptibility. The breakpoints should be decided for each organ since concentration of antibiotics at each infection site differs depending upon location. Breakpoints used in most of the world comprise only one or two breakpoints, thus neglecting the infection site.[3,4]

The NCCLS (National Committee for Clinical Laboratory Standards) breakpoints extensively used in Japan[5,6] were determined on the available data, such as clinical dose and pharmacological kinetics, from American studies and are, therefore, not suitable for Japanese due to differing dose schedules. The breakpoints for Japanese should be investigated on the basis of the clinical dose in Japan (These are set by the Ministry of Health and include maximum allowable dose).

Japan Society of Chemotherapy decided therefore to establish the breakpoints for each infection site based upon the clinical dose used in Japan and the concentration of the drug at the infection site for Japanese patients. In this report, we attempted to analyze the breakpoints for pulmonary infections and sepsis.

## II. CLINICAL BREAKPOINTS IN RESPIRATORY TRACT INFECTIONS

### *1. The concept of breakpoints for antimicrobial agents*

The term breakpoint covers a bacteriological breakpoint that provides information regarding the in vitro sensitivity of bacteria to antibiotics. It also includes a clinical information to assist the physician to assess the clinical response of the patient to selected agents. The breakpoints in this report refer to the latter in-vivo situation.

### *2. Definition of the clinical breakpoint*

The clinical breakpoint is defined as the MIC of antibiotics that is effective in more than 80% of cases, in patients with infectious diseases. The areas covered in this report are respiratory tract infections, divided into lower respiratory tract infections (acute pneumonia) and chronic respiratory tract infections (CRTI). The breakpoints for individual agents were determined for each disorder. Aerobes only were considered due to insufficient clinical data for anaerobes. No further differentiation among bacterial characteristics was made.

### *3. Approach to definition of breakpoints in clinical cases*

Cases were selected from double blind test data for new antibiotics submitted for evaluation by various pharmaceutical companies. Cases were restricted to those for which the clinical response to the agents had been determined and for which the MIC against the isolated bacteria had been measured. The proposed breakpoints for individual antimicrobial agents were based on those data. Tables 2 and 3 contain a partial list of these breakpoints.

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***Table 1.*** *Committee on antimicrobial susceptibility testing.*

| | |
|---|---|
| Sachiko Goto, MD (Former chairman) | Toho University, School of Medicine Department of Microbiology |
| Atsushi Saito, MD (Chairman) | University of the Ryukyus, Faculty of Medicine Department of Internal Medicine I |
| Takashi Inamatsu, MD | Tokyo Metropolitan Geriatric Hospital Infectious Diseases Section |
| Harushige Kanno, MD | Chiba University Hospital Department of Laboratory Medicine |
| Hiromi Kumon, MD | Okayama University, School of Medicine Department of Urology |
| Nobuchika Kusano, MD | Ryukyu University Hospital Central Clinical Laboratory |
| Toyoko Oguri, PhD | Juntendo University Hospital Clinical Pathology |
| Jun Okada, MD | Kanto Teishin Hospital Clinical Laboratory |
| Akira Watanabe, MD | Tohoku University Department of Respirutory Medicine, Institute of Development, Aging and Cancer |
| Kunitomo Watanabe, MD | Gifu University, School of Medicine Institute of Anaerobic Bacteriology |
| Keizo Yamaguchi, MD | Toho University, School of Medicine Department of Microbiology |

***Table 2.*** *Relationship between MIC against causative organisms and clinical response (cephem antibiotics for intravenous use).*

| MIC (μg/ml) | Clinical response in respiratory tract infections | |
|---|---|---|
| | pneumonia (n = 339) | CRTI* (n = 393) |
| ≤ 0.025 | 31/44 (70.5%)† | 52/60 (86.7%) |
| 0.05 | 40/51 (78.4) | 47/53 (88.7) |
| 0.1 | 52/57 (91.2) | 54/70 (77.1) |
| 0.2 | 31/38 (81.6) | 34/42 (81.0) |
| 0.39 | 23/29 (79.3) | 11/14 (78.6) |
| 0.78 | 25/29 (86.2) | 27/33 (81.8)‡ |
| 1.56 | 20/26 (76.9) | 11/17 (64.7) |
| 3.13 | 14/17 (82.4)‡ | 20/32 (62.5) |
| 6.25 | 5/10 (50.0) | 3/15 (20.0) |
| 12.5 | 6/11 (54.5) | 11/17 (64.7) |
| 25.0 | 5/8 (62.5) | 3/5 (60.0) |
| 50.0 | 3/4 (75.0) | 3/7 (42.9) |
| ≥ 100 | 11/15 (73.3) | 12/28 (42.9) |
| | 266/339 (78.5) | 288/393 (73.3) |

* *Chronic respiratory tract infection;*
† *Clinical efficacy;*
‡ *Cut-off points determining the breakpoint.*

***Table 3.*** *Relationship between MIC against causative organisms and clinical response (carbapenem antibiotics).*

| MIC (μg/ml) | Clinical response in respiratory tract infection | |
|---|---|---|
| | pneumonia (n = 56) | CRTI* (n = 119) |
| ≤ 0.025 | 25/26 (96.2%)† | 28/32 (87.5%) |
| 0.05 | 6/7 (85.7) | 3/5 (60.0) |
| 0.1 | 4/4 (100) | 9/11 (81.8) |
| 0.2 | 4/6 (66.7) | 13/13 (100) |
| 0.39 | 7/7 (100) | 14/15 (93.3) |
| 0.78 | 1/1 (100) | 12/14 (85.7)‡ |
| 1.56 | 2/2 (100)‡ | 8/12 (66.7) |
| 3.13 | | 5/11 (454) |
| 6.25 | 0/1 (0) | 0/1 (0) |
| 12.5 | | 1/3 (33.3) |
| 25.0 | 1/2 (50.0) | 0/2 (0) |
| ≥ 50.0 | | |
| | 50/56 (89.3) | 93/119 (73.3) |

* *Chronic respiratory tract infection;*
† *Clinical efficacy;*
‡ *Cut-off points determining the breakpoint.*

### *4. Factors influencing clinical breakpoints*

Table 4 summarizes the factors thought to influence the clinical response to antimicrobial agents. The clinical response of any particular agent will be influenced to a great degree by the activity and concentration of the antibiotic at the site of infection. In addition, pharmacokinetic parameters, such as $C_{max}$ (the maximum blood concentration), $T_{1/2}$ (the terminal half-life of the drug), AUC (area under the curve: a measure of the total amount of antibiotic present over a defined period of time), time above the MIC and protein binding, are also important. The antimicrobial characteris-

***Table 4.*** *Factors influencing the clinical response to antimicrobial agents*

| |
|---|
| Human pharmacokinetics |
| Blood concentration: $C_{max}$, $T_{1/2}$, AUC, time above the MIC, etc. |
| Concentration at the site (or concentration in the specimen) in the healthy person, infected patient, pediatric patient, elderly patient, patient with hepatic and/or renal impairment |
| Protein binding |
| Methods of measurement of drug concentration |
| In vitro drug characteristics |
| Stability of drugs (dependence on culture medium or temperature) |
| Factors affecting MIC: testing methods, component and pH of medium |
| Antimicrobial characteristics |
| Mechanisms of resistance |
| Patient factors |
| Compromised hosts |
| Severity of infection |
| Underlying diseases |
| Invasive medical devices |

***Table 5.*** *Calculation pormula for breakpoints.*

**Breakpoint MIC = $C_m \times t \times R_{tr} \times A$**

where $C_m$ is a factor determined by $C_{max}$;

| | |
|---|---|
| 32 : | $C_{max} > 400$ mg/ml |
| 16 : | $200 < C_{max} \leq 400$ |
| 8 : | $50 < C_{max} \leq 200$ |
| 4 : | $10 < C_{max} \leq 50$ |
| 2 : | $1 < C_{max} \leq 10$ |
| 1 : | $C_{max} \leq 1$ |

$t$ is a factor allowing for half-life differences;

| | |
|---|---|
| 1 : | $T_{1/2} > 3$ hr |
| 0.5 : | $1 < T_{1/2} \leq 3$ |
| 0.25 : | $T_{1/2} \leq 1$ |

$R_{tr}$ is a factor dependent on the ratio $R$ (= maximum concentration at the site /$C_{max}$ ratio);

| | |
|---|---|
| 4 : | $R > 10$ |
| 2 : | $1.2 < R \leq 10$ |
| 1 : | $0.12 < R \leq 1.2$ |
| 0.5 : | $0.012 < R \leq 0.12$ |
| 0.25 : | $R \leq 0.012$ |

$A$ is a factor which takes into account the antimicrobial characteristics;

2 : aminoglycosides
1 : beta-lactams (penicillins, cephems, monobactams, carbapenems) and new-quinolones
0.5 : tetracyclines, macrolides, clindamycins

tics of the drug (bactericidal/bacteriostatic, 'postantibiotic effect' PAE, etc.) and the condition of the host (the defense mechanism being inhibited by underlying disease, use of drugs, certain medical treatments, etc.) should also be taken into account.

Four of these factors, $C_{max}$ (single dose), $T_{1/2}$, infection site concentration and antimicrobial characteristics of the drugs are considered in this report.

### *5. Calculation of the breakpoints*

The four factors mentioned above were taken into account, and a formula was constructed to calculate a value for the breakpoint as shown in Table 5.

### *6. Proposed breakpoints*

The proposed breakpoints for individual antimicrobial agents determined by the formula are listed in Tables 6 and 7. These values correlate well with the clinical re-

***Table 6.*** *Clinical breakpoints for antimicrobial agents in respiratory tract infections (1).*

| Group | Drug | Route | Dose (g) (single) | Breakpoint MIC (μg/ml) | |
|---|---|---|---|---|---|
| | | | | pneumonia | CRTI* |
| Penicillins | ampicillin | iv | 1.0 | 2 | 1 |
| | piperacillin | iv | 2.0 | 2 | 1 |
| | ticarcillin | iv | 1.0 | 2 | 1 |
| | aspoxicillin | iv | 1.0 | 4 | 2 |
| | sulbactam / ampicillin | iv | 1.5 | 4 | 2 |
| | clavulanic acid / ticarcillin | iv | 1.6 | 4 | 2 |
| | ampicillin | po | 0.5 | 0.5 | 0.125 |
| | amoxicillin | po | 0.25 | 1 | 0.5 |
| Cephems | cefazolin | iv | 1.0 | 4 | 2 |
| | cefotiam | iv | 1.0 | 4 | 1 |
| | cefoperazone | iv | 1.0 | 4 | 2 |
| | cefmenoxime | iv | 1.0 | 4 | 2 |
| | cefotaxime | iv | 1.0 | 2 | 0.5 |
| | ceftizoxime | iv | 1.0 | 4 | 2 |
| | cefodizime | iv | 1.0 | 4 | 2 |
| | ceftazidime | iv | 1.0 | 4 | 2 |
| | cefaclor | po | 0.5 | 1 | 0.5 |
| | cefixime | po | 0.2 | 1 | 0.5 |
| | cefpodoxime proxetil | po | 0.2 | 1 | 0.5 |
| | cefuroxime axetil | po | 0.5 | 1 | 0.5 |
| | cefdinir | po | 0.2 | 1 | 0.5 |
| | cefetamet pivoxil | po | 0.5 | 1 | 0.5 |
| | cefprozil | po | 0.25 | 1 | 0.5 |
| | cefotiam hexetil | po | 0.4 | 0.5 | 0.25 |
| | ceftibuten | po | 0.2 | 1 | 0.5 |
| | cefcamate pivoxil | po | 0.2 | 1 | 0.5 |
| | cefteram pivoxil | po | 0.2 | 0.5 | 0.5 |
| | cefditoren pivoxil | po | 0.2 | 1 | 0.5 |
| Carbapenems | imipenem / cilastatin | iv | 0.5 | 1 | 0.5 |
| Monobactams | aztreonam | iv | 1.0 | 4 | 2 |
| | carumonam | iv | 1.0 | 4 | 2 |

* *Chronic respiratory tract infection.*

sponse (more than 80% effective). The breakpoints for some agents, including penicillin G, erythromycin, tetracycline and clindamycin could not be determined because of insufficient or uncertain data.

### *7. Bacteria-specific breakpoints*

The determination of breakpoints for individual bacteria was not attempted in this report. A separate procedure would be necessary in the case of beta-lactamase producing bacteria such as *Moraxella catarrhalis* or *Hemophilus influenzae*, methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae* and anaerobes.

## III. CLINICAL BREAKPOINTS IN SEPSIS

### *1. Subjects and methods*

The subjects were elderly patients from one institution with sepsis due to *Pseudomonas aeruginosa* or *S. aureus*. The measurement of MIC for each organism was performed by the agar dilution method or microdilution broth method based on the standard method of the Japan Society of Chemotherapy. This report focuses mainly on β-lactam agents, and excludes aminoglycosides and new-quinolones due to a lack of sufficient data.

### *2. Design of clinical breakpoints in sepsis*

The P–M ratio (peak blood concentration one hour after intravenous administration of the drug/MIC of bacteria) was calculated in individual cases and compared with the clinical response. The P–M ratio for a clinical efficacy of 80% was defined as the tentative cut-off point. It is assumed that the proposed cut-off point be 1.5 times greater, as the real concentration of the drug in the elderly patients is expected to be 1.5 times that of normal healthy adults.

A clinical response of almost 100% was attained in cases with a P–M ratio of more than 32, decreasing for lesser values. Although this suggests a tentative breakpoint of P/32, the proposed breakpoint was thus modified to P/50.

***Table 7.*** *Clinical breakpoints for antimicrobial agents in respiratory tract infections (2).*

| Group | Drug | Route | Dose (mg) (single) | Breakpoint MIC (μg/ml) | |
|---|---|---|---|---|---|
| | | | | pneumonia | CRTI* |
| Aminoglycosides | gentamicin | iv | 60 | 2 | 2 |
| | tobramycin | im | 60 | 2 | 2 |
| | dibekacin | iv | 100 | 2 | 2 |
| | amikacin | im | 200 | 4 | 4 |
| | sisomicin | im | 75 | 2 | 2 |
| | micronomicin | im | 60 | 2 | 2 |
| | astromicin | im | 200 | 4 | 4 |
| | netilmicin | im | 75 | 2 | 2 |
| | isepamicin | im | 200 | 4 | 4 |
| | arbekacin | im | 75 | 2 | 2 |
| Macrolides | rokitamycin | po | 200 | 1 | 1 |
| | midecamycin | po | 400 | 2 | 2 |
| | roxithromycin | po | 150 | 2 | 2 |
| | clarithromycin | po | 200 | 1 | 2 |
| | midecamycin | po | 600 | 0.5 | 0.5 |
| New quinolones | norfloxacin | po | 200 | 1 | 1 |
| | enoxacin | po | 200 | 2 | 2 |
| | ofloxacin | po | 200 | 2 | 2 |
| | ciprofloxacin | po | 200 | 2 | 2 |
| | tosufloxacin | po | 150 | 1 | 1 |
| | lomefloxacin | po | 200 | 2 | 2 |
| | temafloxacin | po | 200 | 2 | 4 |
| | sparfloxacin | po | 200 | 1 | 2 |
| | fleroxacin | po | 200 | 2 | 2 |
| | levofloxacin | po | 100 | 2 | 2 |
| Tetracyclines | minocycline | po | 100 | 1 | 1 |
| | doxycycline | po | 100 | 1 | 1 |

* *Chronic respiratory tract infection.*

***Table 8.*** *Clinical breakpoints for antimicrobial agents in sepsis.*

| Group | Drug | Route | Dose (g) (single) | Breakpoint MIC (μg/ml) |
|---|---|---|---|---|
| Penicillins | ampicillin | iv | 1.0 | 1 |
| | piperacillin | iv | 2.0 | 1 |
| | ticarcillin | iv | 1.0 | 1 |
| | aspoxicillin | iv | 1.0 | 2 |
| | sulbactam / ampicillin | iv | 1.5 | 2 |
| | clavulanic acid / ticarcillin | iv | 1.6 | 2 |
| Cephems | cefazolin | iv | 1.0 | 2 |
| | cefotiam | iv | 1.0 | 2 |
| | cefoperazone | iv | 1.0 | 2 |
| | cefmenoxime | iv | 1.0 | 2 |
| | cefotaxime | iv | 1.0 | 1 |
| | ceftizoxime | iv | 1.0 | 2 |
| | cefodizime | iv | 1.0 | 2 |
| | ceftazidime | iv | 1.0 | 2 |
| Carbapenems | imipenem / cilastatin | iv | 0.5 | 0.5 |
| Monobactams | aztreonam | iv | 1.0 | 2 |
| | carumonam | iv | 1.0 | 2 |

### 3. Calculation of breakpoints

The breakpoints in sepsis were determined using the formula constructed for calculating the breakpoints in respiratory infections, but modifying $R_{tr}$ to 0.5. The proposed breakpoints in sepsis are listed in Table 8.

It should be cautioned that the proposed breakpoints are not universal, as our study only considered $\beta$-lactam antibiotics in elderly patients irrespective of the bacteria involved.

## IV. CLOSING REMARKS

The present report constitutes the first attempt in Japan to determine breakpoints for antimicrobial agents in pulmonary infections and sepsis. We arrived at the above points after taking several factors into consideration, such as breakpoint designations (high/low or sensitive/resistant), bacterial species, infection sites.

The formula employed in this report to determine breakpoints was derived from results of the most currently reliable test, the double blind test. Consequently, where information was not available, e.g., for antimicrobial agents, such as PCG, EM, CLDM, TC, etc., the breakpoints could not be calculated. Breakpoints are expected to be revised as more reliable basic data become available. Breakpoints for new antimicrobial agents will be calculated using the same formula and reported as these agents are developed.

## ACKNOWLEDGMENT

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